## REMARKS

Applicant requests reconsideration. Claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68 and 71-76 were previously pending and are still pending and under examination in this application.

### Rejections Under 35 U.S.C. §103

Claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 remain rejected under 35 U.S.C. §103(a) as obvious over Rodriguez-Moran et al. (1999) in view of Rohfling C. L., et al. (2000) and Chapin B. L., et al. (1999). According to the Examiner, Rodriguez-Moran teaches that elevated serum CRP levels have been found in type II diabetics and in diabetics with foot ulcers and that elevated serum CRP levels are also found in noncontrolled type II diabetic patients. The Examiner admits that Rodriguez-Moran "does not teach the characterizing [of] a risk profile for developing diabetes in an apparently healthy individual nor evaluating the likelihood that an individual will benefit from treatment."

The Examiner asserts that Rohfling "teaches the use of a screening assay for undiagnosed diabetes and/or complications thereof " referring to page 187 and the Conclusions of the reference. The Examiner also asserts that Chapin "teaches that even apparently healthy individuals who undergo regular physical examination can suffer from undiagnosed diabetes and/or complications thereof " referring to Table 2 in Chapin et al. According to the Examiner, "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made [to] measure serum CRP levels for uses such as characterizing a risk profile for developing diabetes in an apparently healthy individual or evaluating the likelihood that an individual will benefit from treatment given CRP's known association with type II diabetes, as taught by Rodriguez-Moran et al., given that it is well known to measure a known marker for the presence of, or predisposition to, diabetes as taught by Rohfling et al., even in apparently healthy individuals because even apparently healthy individuals can suffer from undiagnosed diabetes and/or complications thereof, as taught by Chapin et al."

The Examiner considered Applicant's arguments submitted in the response filed on May 6, 2008 but did not find them to be persuasive. The Examiner finds Applicant's argument that the

teachings of Rodriguez-Moran cannot be used to render obvious the predictive value of CRP levels of future diabetes to be "curious". The Examiner argues that "if this argument were to be found persuasive then a rejection for lack of enablement would be required given the fact the example in the specification does not show such predictive value." The Examiner alleges that "[a] careful review of the Example reveals that its methodology is so flawed as to render the results meaningless." According to the Examiner, "Table 1 clearly shows that the majority of the "Cases" in the study did not meet Applicant's definition of "apparently healthy". The Examiner refers to the individuals ("Cases") in Table 1 with "History of Hypertension" and "History of Hyperlipidemia" to support his argument that most of the subjects described in the Example of the instant application were not "apparently healthy".

The Examiner further asserts that Chapin describes "asymptomatic individuals whereas the claims are drawn to a method involving apparently healthy individuals." According to the Examiner "[a] review of the specification reveals that apparently healthy individuals is defined as including individuals absent symptoms and previous clinical evidence of disease". According to the Examiner, "[b]efore the tests of Chapin et al. the subjects presented no clinical evidence of disease and, thus, they were included in the study because they were "apparently healthy". Indeed, individuals with known diabetes were excluded from the tests."

Applicant respectfully traverses the rejection. The instant claims are directed at evaluating individuals who do not yet have diabetes and making assessments based on those evaluations. The invention *predicts* the risk of a *future* disorder (diabetes or diabetic complication) *prospectively* (i.e., before the diabetic disorder happens) among *apparently healthy* individuals based on a level of C-reactive protein (CRP).

The Examiner admits that Rodriguez-Moran that does not teach characterizing a risk profile for developing diabetes or evaluating the likelihood that an individual will benefit from treatment."

Applicant reiterates previously presented arguments that Rodriguez-Moran does not and could not address whether the level of CRP is *predictive* of a *future* diabetes or diabetic complications in *apparently healthy* individuals. Rodriguez-Moran did not evaluate individuals who were apparently healthy (i.e., without diabetes). Instead, Rodriguez-Moran compared the

serum levels of CRP in patients with type II diabetes (i.e., after the diabetic disorder happened). Rodriguez-Moran found that patients with type II diabetes have higher levels of CRP compared to healthy controls. Patients with type II diabetes are not apparently healthy and data from such a group cannot be used to make conclusions regarding apparently healthy individuals.

Furthermore, the Rodriguez-Moran study only shows that patients with type II diabetes have elevated CRP levels. This is not proof that elevated CRP levels predict future diabetes. Based on the study of Rodriguez-Moran one of ordinary skill in the art would have known that it is impossible to distinguish whether the elevated CRP levels simply result from the existing diabetic condition, or whether elevated CRP levels are predictive of diabetes because the CRP levels were measured after the diabetic disorder happened. In fact, the teachings of Rodriguez-Moran suggest that elevated CRP might probably be the result of the diabetic condition rather than the cause of the diabetes (see Rodriguez-Moran et al. p. 215 right-hand column):

> "A probable involved pathway could be related to the raising of serum viscosity and shear stress associated to hyperglycemia, producing endothelium dysfunction and inflammation and in this way, increasing cytokines release and thus elevating CRP levels."

Thus, Rodriguez-Moran does not address whether the level of CRP is *predictive* of *future* diabetes in individuals because if the elevation in the levels of CRP is the result of or is caused by the diabetes, the elevated levels of CRP cannot predict future diabetes (i.e., cannot predict diabetes before it happens). Therefore, the teachings of Rodriguez-Moran do not provide a reason or motivation for one of ordinary skill in the art to consider using levels of CRP to predict future diabetes.

The additional teachings of Rohfling and Chapin do not cure the deficiency of the primary reference of Rodriguez-Moran. Rodriguez-Moran in combination with Rohfling and Chapin does not teach or suggest all the claim limitations of instant claims.

Applicant disagrees with the Examiner's characterization of the teachings of Chapin that they are directed to *apparently healthy* individuals. The subjects of Chapin are described as asymptomatic. The subjects in Chapin with asymptomatic diabetes are not apparently healthy as defined in the instant application. Apparently healthy individuals as defined in the specification on

page 9, lines 4-7 are "individuals who have not previously had any clinical evidence of diabetes and who do not otherwise exhibit symptoms of disease. In other words, such individuals, if examined by a medical professional, would be characterized as healthy and free of symptoms of disease."

In fact, when the asymptomatic subjects in Chapin were tested/examined they were found to have clinical evidence of diabetes. The three subjects in Chapin who were characterized as having asymptomatic diabetes were identified as having diabetes because, upon blood glucose testing, they satisfied both the WHO criterion of 2-h glucose concentration $\geq$ 11.1 mmol/l (200 mg/dl) and the ADA criterion of fasting glucose concentration $\geq$ 6.99 mmol/l (126 mg/dl) (See Chapin page 428, middle column). Thus, the subjects with asymptomatic diabetes in Chapin have clinical evidence of diabetes and would not be classified as apparently healthy.

Applicant disagrees with the Examiner's allegation that, even if the above presented argument were to be found persuasive, "a rejection for lack of enablement would be required given the fact that the example in the specification does not show said predictive value" because, according to the Examiner, most of subjects in the study described in the Example were not "apparently healthy". As outlined in the Summary of the Invention and described in the Detailed Description of the Invention, the basis for this invention is evidence from the Women's Health Study (WHS), a large scale, randomized, double-blind, placebo-controlled primary prevention of cardiovascular disease trial of aspirin and vitamin E conducted among 28,000 apparently healthy women (Buring et al., *J Myocard Ischemia* 4; 27-29, 1992). In that trial, baseline levels of CRP were found to predict the future risk of developing diabetes or diabetic complications independent of a large series of other risk factors. Specifically, individuals with the highest baseline levels of CRP were found to have a statistically significant increase in the risk of developing future diabetes after adjusting for body mass index, hypertension, family history of diabetes, exercise frequency, alcohol consumption, hyperlipidemia, smoking, and menopausal status. In the fully adjusted analysis limited to those apparently healthy women with glycosylated hemoglobin levels below 6.0 percent, the relative risks of developing future diabetes for those with baseline levels of CRP from the lowest to highest quartiles were 1.0, 1.3, 4.1, and 4.2 (P-trend < 0.001). See Table 3 which

shows that baseline plasma concentrations of CRP predict in a statistically significant manner risk of diabetes after adjustment for all risk factors.

Thus, the data from the Women's Health Study support the utility of CRP to predict risk of future diabetes among currently healthy and otherwise low-risk individuals as well as among apparently healthy individuals with no prior evidence of disease.

In view of the above arguments, withdrawal of the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as obvious over Rodriguez-Moran in view of Rohfling and Chapin is respectfully requested.

The Examiner also maintained the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as obvious over Schalkwijk et al. (1999) in view of Rohfling et al. (2000) and Chapin et al. (1999). The Examiner states that Schalkwijk teaches that elevated serum CRP levels have been found in type I diabetes. The Examiner asserts that "[w]hile the reference does not specifically teach characterizing a risk profile for developing diabetes or evaluating the likelihood that an individual will benefit from treatment, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made [to] measure serum CRP levels for said uses given CRP's known association with type I diabetes, i.e., it is obvious to measure a known marker for the presence of, or predisposition to a disease."

Applicant respectfully traverses the rejection. The arguments presented above in response to the obviousness rejection of the claims over Rodriguez-Moran are applicable here. As stated above, the instant claims are directed at evaluating individuals who do not yet have diabetes and making assessments based on those evaluations.

Schalkwijk does not, and could not, address whether a level of CRP is predictive of developing diabetes or diabetic complications or whether an apparently healthy individual (i.e., without diabetes) would benefit from prophylactic treatment to prevent diabetes or diabetic complications. Schalkwijk did not evaluate individuals who were apparently healthy (i.e., without diabetes). Instead, Schalkwijk compared the serum levels of CRP in type I diabetic patients (i.e., after the diabetic disorder happened). Schalkwijk teaches that patients with type I diabetes had

higher serum levels of CRP. It should be noted that the study of Schalkwijk was not designed in a manner that would permit one to conclude that elevated levels of CRP predict diabetes. The Schalkwijk study only shows that patients with diabetes have elevated CRP levels. This is not proof that elevated CRP levels predict future diabetes. Based on the data in Schalkwijk, one of ordinary skill in the art would have known that it is impossible to conclude definitively that the elevated CRP levels simply result from the existing diabetic condition, or whether elevated CRP levels are predictive of diabetes because the CRP levels were measured after the diabetic disorder happened. In fact, the teachings of Schalkwijk suggest that elevated CRP is more likely the result of the diabetic condition rather than the cause of the diabetes (see Schalkwijk p. 356):

> "Various possible mechanisms could induce chronic low degree inflammation in diabetes, including activation of macrophages, increased oxidative stress or an induction of cytokines. One of the pathophysiological consequences of hyperglycaemia is the phenomenon of nonenzymatic glycation and the formation of advanced glycation end products (AGEs). AGEs have been shown to activate macrophages, to increase oxidative stress and to induce, in macrophages, the synthesis of interleukin-1 and tumor necrosis factor-α and, in vivo in mice, the expression of interleukin-6 mRNA. Many of the possible mechanisms leading to chronic low degree inflammation could be related to nonenzymatic glycation. Another possibility is that increases in CRP are related to adipose-tissue-derived cytokines." (Citations omitted)

Thus, Schalkwijk does not address whether the level of CRP is *predictive* of diabetes in *apparently healthy* individuals because if the elevation in the levels of CRP is the result of or is caused by the diabetes, the elevated levels of CRP cannot predict future diabetes (i.e., cannot predict diabetes before it happens). Therefore, Schalkwijk is incapable of providing a basis for one of ordinary skill in the art to conclude that elevated CRP is a risk factor for developing diabetes in the future. Accordingly, the teachings of Schalkwijk do not render the claimed methods obvious.

In view of the above arguments, withdrawal of the rejection of claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68, and 71-76 under 35 U.S.C. §103(a) as obvious over Schalkwijk in view of Rohfling and Chapin is respectfully requested.

## CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: January 9, 2009

Respectfully submitted,
***Ridker et al., Applicant***

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